Study: Kamel et al (2007)

Quality: Moderate (7 pts)					
D 2	E 1	O 1	C 1	A 1	B 1

F Kamel, CM Tanner, DM Umbach, JA Hoppin, MCR Alavanja, A Blair, K Comyns, SM Goldman, M Korell, JW Langston, GW Ross, DP Sandler; Pesticide Exposure and Self-reported Parkinson's Disease in the Agricultural Health Study. Am J Epidemiol 2007, 165 (4): 364-374.

STUDY SUMMARY

Study Overview

The Agricultural Health Study (AHS) cohort is used to assess the association of pesticide exposure and Parkinson's disease (PD). The AHS cohort was enrolled in 1993-1997, and follow-up interviews were conducted 1999-2003. Subjects were pesticide applicators and their spouses. At enrollment, subjects provided detailed information on lifetime pesticide use. At enrollment and follow-up, questionnaires elicited a response to whether the subject reported a physician diagnosed PD. There were 83 reported enrollment PD cases (prevalent cases) and 78 reported follow-up PD cases (incident cases). Incident PD was associated with cumulative days of pesticide use (p=0.009). Prevalent PD was not associated with overall pesticide use. The study suggests that exposure to certain pesticides may increase PD risk. Potential herbicides associated with PD are pendimethalin, paraquat, cyanazine, dicamba, trifuralin, 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), and butylate, though only cyanazine attained statistical significance and only for prevalent PD. Potential other pesticides associated with PD are: the fumigants, carbon disulfide/carbon tetra-chloride, ethylene dibromide, and methyl bromide; the insecticides, lindane and phorate; and the fungicides, chlorothalonil and benomyl. Paraquat was found to be marginally associated with prevalent PD (OR, 1.8; 95% CI, 1.0-3.4), but not associated with incident PD (OR, 1.0; 95% CI, 0.5-1.9).

Study Details

Study Participants. Study participants are from the AHS cohort. At enrollment, 52,393 private applicators completed a self-administered enrollment questionnaire. Most enrollees were married, and 32,345 of their spouses enrolled in the study by completing a spouse questionnaire. Hence, there were 84,738 subjects at enrollment. The enrollment questionnaires elicited information on pesticide use, demographic factors, lifestyle, and medical history, including physician-diagnosed PD.

Five years after enrollment, 57,251 cohort members (68% of 84,738 enrollment cohort) completed a follow-up questionnaire. Information from the follow-up interviews used for analysis was self-reported physician-diagnosed PD, age at diagnosis, age at interview, and smoking status.

Exposure Measurement. The initial exposure measurement is 'ever use of any pesticide', where 82 percent of enrollment subjects indicated yes. The ever pesticide use was further broken down to mixing pesticides (categorized as no, <50% time, ≥50% time, and missing) and applying pesticides (also categorized as no, <50% time, ≥50% time, and missing). The ever pesticide use was further reported by duration (in years) and frequency (days per year) of use of any pesticide. Cumulative days of use of any pesticide was the product

of duration and frequency, categorized by quartiles. Finally, the ever use of pesticide was further dichotomized by ever use of 50 commonly used pesticides; one the 50 was paraquat.

Additional exposure measurements are 'use of personal protective equipment', 'pesticide related medical care', and 'washing after a high personal exposure event'. Applicators provided information on use of types of personal protective equipment (e.g., chemical-resistant gloves), and from these responses 'use of personal protective equipment' was categorized as low protection, moderate protection, high protection, or missing. For applicators, information on pesticide-related medical attention was collected using the question, 'As a result of using pesticides, how often have you seen a doctor or been hospitalized?' Responses were categorized as no, yes, or missing. Based on two questions, 'washing after a high personal exposure' was categorized as no event, washed within 1 hour, washed after 1 hour, or missing.

Outcome Ascertainment. At enrollment and follow-up subjects were asked, 'Has a doctor ever told you that you had been diagnosed with Parkinson's disease?'. There were 83 self-reported enrollment PD cases (prevalent cases). A small number of possible cases were excluded due to inconsistent responses (e.g., responding yes at enrollment and no at follow-up). There were 78 self-reported follow-up PD cases (incident cases). These incident cases were first diagnosed with PD after enrollment and before follow-up (by responding no or missing at enrollment and yes at follow-up).

Methods of Analysis. Logistic regression was used to evaluate the relation of either prevalent PD or incident PD to general pesticide variables. Models included adjustment for age at enrollment; state (Iowa or North Carolina); and type of participant (applicator or spouse).

Confounders Considered. Models included adjustment for age at enrollment; state (Iowa or North Carolina); and type of participant (applicator or spouse). Most applicators were men (>99 percent) and most spouses were women (96 percent), so no adjustment was made for gender. Other confounders considered were race, education, and smoking.

Effect Measure and Point Estimates. Paraquat was found to be marginally associated with prevalent PD (OR, 1.8; 95% CI, 1.0-3.4), where 14 of the 83 prevalent PD cases where known to have ever used paraquat. However, paraquat was not associated with incident PD (OR, 1.0; 95% CI, 0.5-1.9), where 11 of the 78 incident PD cases where known to have ever used paraquat.

Strengths and Limitations Discussed in the Paper. A notable strength of the study is the use of AHS, a large sample from an agricultural population with many pesticide exposed subjects. Other strengths noted in the paper include, distinguishing between prevalent and incident cases, representation of diverse farming practices (Iowa v NC), and subjects providing detailed exposure data (including 50 specific pesticides).

At enrollment, subjects and prevalent PD cases with high pesticide exposure may have been less likely to enroll in the study than those with lower exposure, because PD or other effects of pesticide exposure led them to stop farming at an earlier age prior to

possible enrollment. The questionnaires focused on lifetime pesticide use; where pesticide use may decrease over time due to earlier health effects. Among other limitations noted are the self-reporting of PD and pesticide usage, the challenge of concurrently considering multiple pesticides, potential bias due to only 68% subjects from enrollment completing follow-up, and lacking date of diagnosis for prevalent PD cases (hence unknown duration of PD at enrollment). Finally, though not explicitly acknowledged, the authors were aware that subset analyses (e.g., separate analyses by applicator and spouse or by smoking status) lacked statistical power.

EVALUATION

This study design consists of two parts: the enrollment data forms a retrospective cohort substudy to investigate association of lifetime pesticide use with current PD status (i.e., prevalent PD). With the addition of follow-up interviews, the second part is a prospective cohort substudy to investigate association of lifetime pesticide use with onset of PD (i.e., incident PD). While the enrollment cohort is large (84,738 subjects), PD is a relatively rare disease (83 prevalent cases and 78 incident cases). Hence, the statistical power is low.

Logistic regression is an adequate analytic methodology. The authors elected to use a two-stage hierarchical logistic regression to increase precision (Witte et al, 2000). Conceptually, this two-stage model makes sense, i.e., pesticides classified by functional groups (e.g., insecticides, herbicides, etc.) and by chemical groups (e.g., organophosphates, etc.) form a second stage hierarchy of specific pesticides. However, no results are shown to demonstrate any increased precision. Further, the resulting Bayesian analysis uses a prior residual variance of 0.35 as suggested by Witte et al. (2000). No justification for this residual variance selection is provided.

The categorization of all demographic variables (e.g., age as 12-50, 51-60, 61-70, 71-92) was found reasonable. The categorization of exposure variables (e.g., cumulative lifetime days of pesticide use as 0-64, 65-200, 201-396, ≥397) was also found reasonable. Although, in a supplemental regression model, cumulative days of pesticide use was used as a continuous covariate defined by the midpoints of the levels in the categorical variable. First, there appears to be no reason why the actual days could not have been used, and second, the midpoint of the interval ≥397 days is not clear.

Since the date of PD diagnosis between enrollment and follow-up is known, an alternative analysis on the follow-up data could have been a Poisson regression. Also, 25 subjects with possible prevalent PD were excluded from analysis; 12 subjects excluded due to conflicting responses on enrollment questionnaires, and 13 subjects excluded due to denial of PD on follow-up questionnaire.

Finally, self-reporting pesticide use and PD diagnosis was noted by the authors as a limitation. The authors cite other studies that have found AHS self-reporting to be reliable. Although, using the National Death Index the authors identified 61 persons listing PD as an underlying or contributing cause of death. There were 35 of these 61 persons that did not self-report PD at enrollment or follow-up.

REFERENCES CITED

Witte JS, Greenland S, Kim LL, et al. Multilevel modeling in epidemiology with GLIMMIX. Epidemiology 2000, 11:684–8.